EDITORIALS

The Choice of Antipsychotic Drugs for Schizophrenia

Robert Freedman, M.D.

Since the discovery of the effects of chlorpromazine in the 1950s, treatment of schizophrenia has relied on antipsychotic drugs that target dopamine D2 receptors. The effectiveness of these agents in reducing the intensity of patients' delusions and hallucinations permitted outpatient treatment instead of lifelong institutionalization in state mental hospitals. The many antipsychotic drugs introduced during the next decade were increasingly potent, as medicinal chemists improved the drugs' affinity for the D2 receptor. However, the efficacy of the drugs was similar, since all had the same mechanism of action.[1] A troubling problem was that the blockade of dopaminergic neurotransmission in the basal ganglia caused parkinsonian syndromes. A long-lasting movement disorder, tardive dyskinesia, also occurred with prolonged treatment. More fundamentally, the early promise that these drugs might dramatically improve patients' psychosocial and cognitive disabilities was only partially fulfilled.[2] Although many mental hospitals were closed, mental health centers were filled with outpatients who could not live successfully in their communities.

By the early 1970s, the European experience with one drug, clozapine, suggested that it might be significantly more effective than other antipsychotic drugs and that it did not cause movement disorder to the same degree as the others. Clozapine indeed proved to be more effective at reducing symptoms than other neuroleptic agents.[3] However, the potential of clozapine to cause toxic side effects, including agranulocytosis, has limited its prescription to about 10 percent of persons with schizophrenia. Clozapine was labeled an atypical antipsychotic agent because it caused less movement disorder than other antipsychotics. The mechanism of action of clozapine differs in many ways from that of other dopamine D2 receptor antagonists; the most popular hypothesis is that it has weaker D2 antagonism and stronger antagonism at serotonin 5-hydroxytryptamine$_{2A}$ receptors.[4] Pharmaceutical companies, acting on this hypothesis, have developed new drugs, attempting to capture the enhanced therapeutic effect of clozapine without its toxicity. The resultant second generation of drugs now accounts for the majority of antipsychotic drugs prescribed for all psychiatric uses, including schizophrenia.

Concerns have emerged about this new generation of drugs. First, although clozapine was introduced after studies indicated that it had more efficacy than first-generation drugs, the other new antipsychotic agents were marketed after studies showed efficacy that was only comparable to that of older drugs. Thus, the issue of whether they, like clozapine, were truly more effective remained largely unanswered. Second, although the newer drugs fulfilled their promise of causing less movement disorder, new problematic side effects — severe weight gain, often accompanied by type 2 diabetes mellitus and hypercholesterolemia — emerged.[5,6] Weight gain had occurred with the older drugs, although it was generally less substantial. Third, the cost of newer medications caused payers to question their purported value. Therefore, the National Institute of Mental Health undertook a multisite, double-blind comparison between an older drug, perphenazine, and a series of the newer drugs; clozapine was omitted because it had already been observed to have superior efficacy. The results of this work, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), are reported in this issue of the *Journal*.[7]

What to measure in such a trial is itself problematic. Schizophrenia is a chronic disability of mental and social function, with superimposed episodes of exacerbated psychotic symptoms. In addition to hallucinations and delusions, affected

patients have characteristic neuropsychological difficulties, including problems in paying attention, learning new information, and recognizing social cues, such as the emotional meaning of facial expressions. Their social isolation, loss of sense of pleasure, inability to make decisions, and poor self-care forms a third symptom complex. Patients who carry the diagnosis of schizophrenia vary markedly in these various aspects of their illness. Efficacy is therefore difficult to measure. The time to discontinuation of medication for any reason — a side effect, poor efficacy, or the patient's decision about adherence — was the principal outcome variable in CATIE. Its advantage as a primary measure is that it is relatively definable and less subject to the vicissitudes of patients' descriptions of their symptoms and the perception of these symptoms by others, even those trained in assessing them. CATIE used a single scale, the Positive and Negative Syndrome Scale (PANSS), to rate patients' symptoms as a secondary outcome. Side effects were recognized as an important issue in the design of CATIE.

The results could be viewed as discouraging. No drug provided the majority of patients a treatment that lasted the full 18 months of the study. Thus, treating schizophrenia, even with new-generation drugs, is only partially effective and is associated with problematic side effects. Only 36 percent of the patients receiving the most effective drug, olanzapine, completed the trial. Twenty-five percent of those receiving perphenazine completed the trial. Patients receiving other second-generation antipsychotic drugs — quetiapine, risperidone, and ziprasidone — did no better than those receiving perphenazine. Thus, there was a small improvement with olanzapine as compared with the first-generation drug perphenazine, but this advantage was not observed with the other second-generation drugs. This difference was reflected in the other clinical measurements, including PANSS ratings. The greater efficacy of olanzapine, as compared with that of these other drugs, is consistent with the results of a recent meta-analysis.[8] However, olanzapine was also associated with notable metabolic effects. Thirty percent of the patients receiving olanzapine gained more than 7 percent of their body weight during the trials, as compared with 7 to 16 percent of those receiving the other drugs. There were comparable problems revealed in measured blood glucose, cholesterol, triglyceride, and glycosylated hemoglobin levels.

Thus, the patient with schizophrenia and his or her doctor face difficult choices. Two drugs, olanzapine and clozapine, appear to be more effective than other agents. However, both drugs induce a significantly greater number of serious side effects. Even the most feared side effect of first-generation drugs, tardive dyskinesia, seems less troubling than potentially fatal metabolic problems. Does the apparently moderate increase in the efficacy of olanzapine and clozapine justify the use of these agents for treating patients? The answer to this question is a matter of clinical judgment and informed patient preference. Most clinicians offer patients several possibilities over the course of their illness.

Few clinicians offer patients first-generation drugs initially because the immediate problems with movement disorder are associated with poor adherence. The relative absence of side effects with risperidone, quetiapine, and ziprasidone make them frequent choices for initial treatment for many patients. However, over the duration of the illness, it is striking that olanzapine and clozapine often result in an increase in cognition that can lead to alterations in its course, although in some patients these improvements occur with other drugs as well.[9,10] With these agents, patients resume vocational and social interests that seemed irretrievably lost early in the course of their illness. Heavy cigarette smoking often remits during treatment with olanzapine and clozapine, indicating decreased reliance on the effects of nicotine.[11] Because metabolic problems are likely to occur, dietary and exercise counseling should be introduced before the initiation of treatment with these two drugs.

Although no one postulates that the biologic effects of clozapine and olanzapine are permanent, the positive effects often persist when, because of metabolic effects, treatment is switched to other second-generation or even first-generation drugs. CATIE does not capture all these clinical points, but it provides data consistent with these clinical observations. It would thus seem reasonable to try olanzapine and clozapine in any patient with schizophrenia who has not had a full clinical remission of the illness, which includes the reversal of cognitive and psychosocial disabilities. However, it is also prudent to switch treatment from these drugs to one of the others if a metabolic syndrome is threatening the patient's general health.

The problem of which antipsychotic agents to use is particularly poignant for patients with childhood-onset schizophrenia. These young patients, who are often initially referred to pediatricians for

school problems, begin experiencing hallucinations and delusions before the age of 13 years.[12] Olanzapine is frequently the medication that provides optimal remission of their mental symptoms. A child who is less disturbed, despite the nearly inevitable massive weight gain, appears at least at first to have a better outcome. However, as the obesity continues to increase over a period of several years, affected children and families eventually ask to switch to other drugs, to restore normal weight, even at the cost of exacerbated psychosis.

Of course, new drugs that do not have metabolic side effects but that do confer the antipsychotic effects of clozapine and olanzapine would be desirable. Just as the second generation of drugs moved beyond D2 antagonism, aripiprazole — a partial agonist at dopamine D2 receptors that facilitates low levels of receptor activation while blocking higher levels — as well as other new drugs in development have mechanisms that move beyond the dopamine D2–5-hydroxytryptamine$_{2A}$ hypothesis. How these drugs perform in comparison with olanzapine is still unknown. The value of CATIE is that it provides solid evidence to help clinicians and their patients make the difficult decisions needed to optimize the treatment of schizophrenia with the compounds currently available.

From the Department of Psychiatry, University of Colorado Health Sciences Center, and the Veterans Affairs Medical Center — both in Denver.

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